A Phase 1, Open-Label, Dose Escalation and Dose Expansion Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Anti-Tumor Activity of PF-07799544 (ARRY-134) as a Single Agent and in Combination With PF-07799933 BRAF Dimer Inhibitor, in Participants 16 Years and Older With Advanced Solid Tumors

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Objective

- To investigate the safety, tolerability, pharmacokinetics, pharmacodynamics, and potential clinical benefits of PF-07799544 (ARRY-134) given as a single agent in participants with advanced solid tumors (phase 1a) and in combination with PF-07799933 in participants with BRAF class I, II, and III mutated solid tumors with or without brain involvement (phase 1b) (NCT05538130).

Conclusion

- Recruitment is open at centers in the USA and Canada, and planned in Israel.

Background

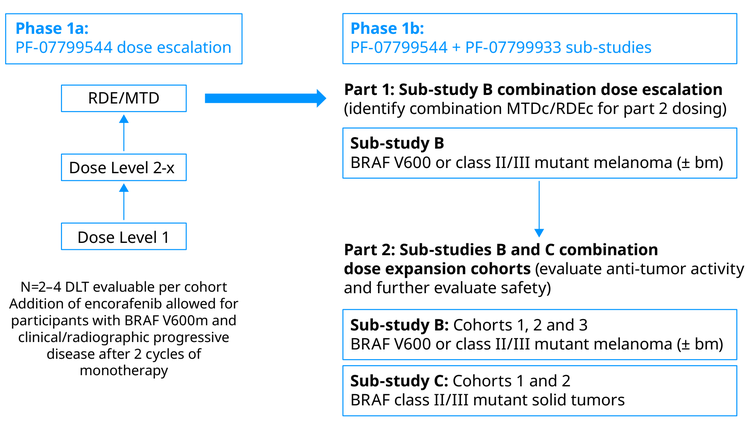
- The mitogen-activated protein kinase (MAPK) pathway plays a role in several key signaling and phosphorylation events that contribute to tumorigenesis.[1] Inhibition of MEK, along with RAF kinases, has proven to be a successful transformative strategy for melanoma and other MAPK pathway–altered tumors.[2] However, the duration of clinical benefit is limited by a narrow therapeutic index, de novo and acquired resistance, and poor brain penetration.[3,4]
- PF-07799544 is a next-generation, fully brain penetrant MEK inhibitor. Therefore, there is a strong scientific rationale for PF-07799544 as a backbone for targeted therapy combinations.
- Approved B-type RAF proto-oncogene (BRAF) inhibitors have transformed the treatment landscape for BRAF V600 mutant cancers but suffer 3 key liabilities: limited brain penetrance, BRAF dimer-promoting resistance mutations, and toxicity from paradoxical signaling activation in BRAF wild-type cells.[5-7]
- PF-07799933 is a next-generation oral selective ATP-competitive small-molecule brain-penetrant BRAF-selective monomer/dimer inhibitor that suppresses BRAF signaling in BRAF V600 mutant and non–V600 BRAF mutant tumors. It displays significantly less paradoxical activation than approved BRAF inhibitors and is not 'pan RAF', as it spares non–BRAF mutated-containing RAF dimers.
- Here we describe the design of the phase 1 study of PF-07799544 as monotherapy or in combination with PF-07799933 in participants with BRAF mutated (BRAFm) advanced solid tumors.

Methods

STUDY DESIGN

- This is a first-in-human, open-label, phase 1a/b study of PF-07799544 (ARRY-134) as a single agent and in combination with PF-07799933 in participants with advanced solid tumors.
- Phase 1a is a monotherapy dose escalation of PF-07799544 enrolling ~40 participants who have progressed on standard of care (**Figure 1**).
  - The primary objective is to determine monotherapy maximum tolerated dose (MTD)/recommended dose for expansion (RDE) of PF-07799544. Once pharmacokinetic measurements indicate the potential for significant wild-type MEK mutation target coverage, participants with untreated and symptomatic brain metastases (bm) will be allowed to enroll.

Figure 1: Study design



bm=brain metastases; BRAF=B-type RAF proto-oncogene; DLT=dose-limiting toxicity; MTDc=maximum tolerated dose combination; RDEc=recommended dose for expansion combination

- Phase 1b involves participants with BRAFm solid tumors who have progressed on standard-of-care therapies, including class I BRAFi, where indicated. It involves multiple sub-studies in 2 parts to evaluate PF-07799544 in combination with PF-07799933 (**Figure 1**).
  - Part 1 sub-study B combination dose escalation involves patients with BRAFm melanoma (V600 and non-V600).
    - Part 1: combination dose escalation: primary objective is to determine the MTDc/RDEc of the combination.
  - Part 2: combination dose expansion (~80 participants): primary objective is to evaluate preliminary anti-tumor activity and further evaluate safety of the combination. Sub-study B dose expansion cohorts include:
    - Cohort 1: BRAF V600 melanoma (asymptomatic and untreated bm permitted)
    - Cohort 2: BRAF V600 melanoma (symptomatic bm)
    - Cohort 3: BRAFm class II/III melanoma (asymptomatic and untreated bm permitted).
- Sub-study C involves patients with BRAFm class II/III advanced solid tumors.
  - Sub-study C will commence after identification of the combination MTDc/RDEc in sub-study B part 1.
  - Sub-study C dose expansion (~20 participants each cohort):
    - Cohort 1 (asymptomatic and untreated bm permitted)
    - Cohort 2 (symptomatic bm).
- Key patient inclusion and exclusion criteria are shown in **Table 1**.

Table 1: Key patient inclusion and exclusion criteria

Key inclusion criteria	Key exclusion criteria
Age ≥16 y	Brain metastasis larger than 4 cm
ECOG performance status 0–1[a]	Brain metastasis/primary brain tumor requiring immediate local intervention in the opinion of the investigator on C1D1
Adequate bone marrow, renal, and liver function	Active malignancy within 3 years prior to enrollment[b]
Resolution of acute effects of any prior therapy to either baseline severity or CTCAE grade ≤1	Active, uncontrolled bacterial, fungal, or viral infection including (but not limited to) HBV, HCV, and known HIV or AIDS-related illness
Diagnosis of advanced/metastatic solid tumor including primary brain tumor. Disease progressed during/following last prior treatment and no satisfactory alternative treatment options (phase 1a)	History or current evidence of retinal vein occlusion or concurrent neuromuscular disorder associated with elevated creatine kinase
Brain metastases smaller than 4 cm (phase 1a)	Current use of any prohibited concomitant medication(s)
Documentation of MAPK pathway alteration status (phase 1a)	Systemic anticancer therapy (approved or investigational) ongoing at the time of study entry
Histological or cytological diagnosis of advanced/metastatic melanoma (sub-study B)	Major surgery (eg, inpatient procedure with general anesthesia) within 28 days prior to study entry
Unresectable or advanced/metastatic solid tumor progressed on, or with demonstrated intolerance to SOC, excluding melanoma (sub-study C)	Minor surgical procedure or craniotomy within 14 days prior to study entry; ongoing surgery-induced complications
Measurable disease by RECIST version 1.1 (sub-studies B and C)	Full-dose, external beam radiation therapy within 14 days prior to study entry; ongoing radiation-induced complications
Evidence of a BRAF V600 mutation or BRAF class II/III alteration in tumor tissue and/or blood (sub-study B)	
Evidence of a BRAF founder alteration (non-V600 class II/III BRAF alteration) (sub-study C)	

[a] ECOG performance status 2 may be enrolled with sponsor approval if documented to be due to underlying cancer. [b] Except adequately treated basal cell or squamous cell skin cancer, carcinoma in situ, Bowen's disease, prostate intraepithelial neoplasm, and ≤6 Gleason grade prostate cancer.
C1D1=Cycle 1 Day 1; CTCAE=Common Terminology Criteria for Adverse Events; ECOG=Eastern Cooperative Oncology Group; HBV=hepatitis B virus; HCV=hepatitis C virus; SOC=standard of care

- The primary and secondary endpoints are shown in **Table 2.**

Table 2: Study endpoints—phase 1a and 1b

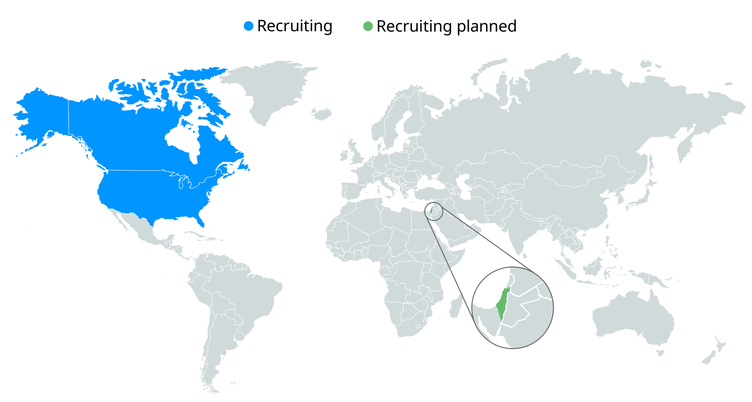
Primary	Dose-limiting toxicities
	Overall response rate by RECIST version 1.1 (phase 1b only)
	Treatment-emergent adverse events
Secondary	Single- and multiple-dose pharmacokinetic parameters
	Treatment-emergent adverse events
	Overall response rate by RECIST version 1.1
	Duration of response overall and in CNS
	Intracranial response by RECIST version 1.1 (for brain metastases) (phase 1b part 2)
	Progression-free survival

CNS=central nervous system

STUDY STATUS

- The study began enrolling patients in November 2022.
- Recruitment is open at centers in the USA and Canada and planned in Israel (**Figure 2**).

Figure 2: Study sites



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